Remarks

Claim 23 is pending in this application.

Claim Rejection Under 35 USC § 112, Second Paragraph

Claim 23 is rejected under 35 USC § 112, Second Paragraph as being indefinite. In particular, the Examiner points out that the term "treatment of disease" as recited in the claim is ambiguous and may have multiple interpretations. Applicants have amended the claim by removing the term "treatment of disease". Claim 23 now recites that the claimed method inhibits apoptosis in a patient afflicted with prion disease.

Applicants respectfully submit that this rejection has been overcome and notice to that effect is requested.

Claim Rejection Under 35 USC § 112, First Paragraph

Claim 23 is rejected under USC § 112, First Paragraph as failing to comply with the written description requirement.

The Examiner states in the Office Action on pages 3-4 that the term "prion" disease written in the specification is found amongst a "laundry list" of seventy five other diseases and that the specification does not contain an actual reduction to practice. The rejection is traversed for the following reasons.

In the prosecution of the instant application, the Examiner required an election of species to a single disclosed method, i.e., a specific disease. Applicants responded with an election of the prion disease. The claimed invention in its broadest sense on page 12 of the specification and previous pending claim 21 relates to a treatment for pathologies associated with abnormal apoptotic activity, hence the inclusion of the seventy five diseases. Applicants were required to make an election of a single disease forcing them to cancel claim 21 and prosecute pending claim 23. It is improper for the Examiner to argue now that we chose this particular disease out of a laundry list of diseases since this was the Examiner's requirement and not the preferred embodiment that Applicants wished to prosecute. Furthermore, it is also improper to reject the claimed invention for lacking written description because the specification fails to show an actual reduction to practice. A constructive reduction to practice by the writing and filing of the application may also fulfill the written description requirement. At the time of the application filing, Applicants were in possession of the claimed invention. The description in the specification on pages 12-14 supports the claim,

describing in sufficient detail how one skilled in the art may administer an effective amount of the tetrahydropyridine compound and which patients would be best served by its administration.

Finally, with regards to the arguments presented in the Office Action on page 4, Applicants submit that the written description requirement does not require Applicants to know the exact mechanism of a neurodegeneration associated with prion disease. All that is necessary is for the skilled artisan to know is a correlation between the functional characteristic of increasing TGF-β1 levels in the treatment of prion disease by use of the instant described tetrahydropyridine compounds. Applicants enclose with this paper three scientific articles (Neurobiology of Disease (2006) 22, 638-650; Neuropathology and Applied Neurobiology (2002) **28**, 107-119 and Molecular Neuroscience (2004) **15**, 2233-2236) linking increased TGF-β1 levels to prion disease.

The Examiner points to the Tashiro et al reference (Neruorpath. Appl. Neruo. (1998) **24**, 284-292) as an indicator of how the prior art fails to show a correlation between TGF-beta 1 and prior disease. We are directed to page 287 of the reference where the authors state immunostaining for TGF-β1 gave inconsistent results among the cases examined with prion diseases. However, the Examiner fails to acknowledge the authors' explanation of this finding in the discussion section of the article on page 291, left column. The pertinent section is reproduced below without the reference citations.

> "In Alzheimer's disease, published reports have described immunoreactivity to TGF-β1 and β2 in senile plaques. In addition, more TGF-β1 messenger RNA was detected in post-mortem brain tissue of Alzheimer's disease patients than in controls. Although we used the same antibodies and the same microwaved method for TGF-βs immunostaining which were reported by the recent studies, senile plaques were negative for TGF-β1 and β2 as well as TGF-β3 and TGF- RII in our study. Autopsy intervals and fixation conditions for our study were also similar to those of the published reports. **We can not exactly explain the cause of this discrepancy, but it might be due to the immunohistochemical protocols including difference in the secondary antibody or the subsequent ABC method.**"
>
> [Emphasis added]

It is clear from this conclusion that the lack of a conclusive correlation between the positive cases for TGF-β1 and prior disease was due to problems in the immunostaining procedure. Hence, this reference cannot be used to indicate that no correlation exists.

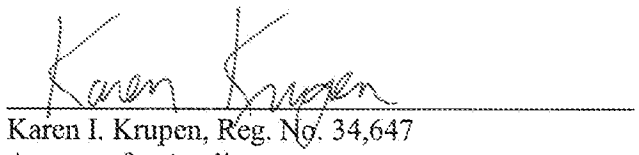
Claim 23 is rejected under the same section, USC § 112, First Paragraph, as failing to comply with the enablement requirement. The Examiner employs the *Wands* factors to make the argument that undue experimentation would be required to practice the claimed invention. This rejection is traversed for the following reasons.

First, the state of the art cannot be demonstrated by the Tashiro reference. As argued in the previous rejection for lack of written description, the lack of a conclusive correlation between the positive cases for TGF-β1 and prior disease was due to problems in the immunostaining procedure. Applicants have provided with this paper three references that positively demonstrate a correlation between TGF-β1 and prior disease. Second, with respect to a lack of working examples, Applicants have provided a range of administration doses that depends on the weight of the patient and the degree of advancement of the disease on page 13, lines 22-35. The disclosed protocols provide a reasonable amount of guidance to the skilled artisan to make and use the claimed invention without undue experimentation, even though considerable work may be required because there is still much to be learned about the mechanism of action of this disease.

Accordingly, Applicants submit that the claim invention is supported and enabled by the specification and that the instant specification describes the invention as claimed. Thus, withdrawal of the rejection is in order and respectfully requested.

Should the Examiner believe that an interview would advance the prosecution of this application, the Applicants invite her to contact the undersigned at 908.231.4658.

Respectfully submitted,



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